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The evolutionary theory of senescence underpins research in life history evolution and the biology of aging. In 1957 G.C. Williams predicted that higher adult death rates select for earlier senescence and shorter length of life, but pre-adult mortality doesn't matter to evolution. This was subsequently interpreted as predicting that senescence should be caused by 'extrinsic' sources of mortality. This idea still motivates empirical studies, even though formal, mathematical theory shows it is wrong. It has nonetheless prospered because it offers an intuitive explanation for patterns observed in nature. We review the flaws in Williams' model, explore alternative explanations for comparative patterns that are consistent with the evolutionary theory of senescence and discuss how hypotheses based upon it can be tested. We argue that focussing on how sources of mortality affect ages differently offers greater insight into evolutionary processes.

Williams' theory of senescence

The **Evolutionary Theory of Senescence** (see Glossary) underpins research in life history evolution and the biology of aging. Building on earlier theory [1-3], G.C. Williams published his foundational paper on this subject in 1957 [4]. He presented nine predictions that followed from verbal arguments (but no mathematical models), including his famous '**antagonistic pleiotropy**' model of aging. Another influential prediction, and one that still motivates empirical studies to this day, is that higher adult death rates select for earlier senescence and shorter length of life. As Williams also argued that juvenile mortality has no influence on the evolution of senescence, his theory was subsequently interpreted to predict that senescence should be correlated with **extrinsic mortality**, or causes of death that are independent of age [5]. However, formal, mathematical theory [5-8] shows that this particular prediction is wrong. Some have attempted to defend Williams' extrinsic mortality hypothesis against this criticism [e.g., 9], but we argue in this Opinion that the comprehensive model of natural selection articulated in his 1957 paper is incorrect, and many subsequent studies, citing Williams, rest on a misunderstanding of how mortality shapes evolution.

This formal theory shows that only mortality that is age-specific can influence the evolution of senescence, and the evolutionary consequences depend upon the age at which mortality is expressed. Nevertheless, Williams' model is still cited to explain numerous comparative observations (Table 1), including why flying vertebrates (birds and bats) live much longer than terrestrial vertebrates of the same body size, why poisonous animals live longer than non-poisonous ones and why armored animals live longer than related taxa that lack shells [10].

We believe that Williams' flawed idea has prospered because it offers an intuitively appealing, if wrong, explanation for patterns that are widely observed in nature. Here, we build on W.D. Hamilton's formal mathematical formulation of the evolutionary theory of senescence [11] to review the conceptual error in Williams' verbal model. We explore alternative explanations for comparative patterns consistent with Hamilton [11] and discuss how hypotheses based upon it can be tested, and illustrate diverse specific empirical cases consistent with the formal evolutionary theory of senescence (Table 1). It is our hope to stimulate new empirical research into understanding the ecology of age-specific mortality in natural populations.

The flaw in Williams' model

Williams' prediction follows from P.D. Medawar's (1952) intuitive conjecture that the strength of selection for some age-specific trait should be proportional to the probability that an individual survives to that age [3]. Medawar assumed (erroneously, as we note below) that selection at some late age would be low if few individuals survive to that age, but actually the force of selection must decline with age even in immortal populations [8]. It has long been known that the addition of age-independent mortality can have, by definition, no effect on age distributions [12]. It follows that mortality that is truly independent of **condition** will not affect within- or among-age distributions of phenotypes. Given that phenotypic selection is the covariance between phenotypes and relative fitness [13], and relative fitness is also phenotype [14, 15], it must also be that the strength of selection is insensitive to the addition of extrinsic mortality [5, 16].

A formal proof of Williams' error follows from theory developed by W.D. Hamilton (1966) [11]. Hamilton provided the first rigorous and quantitative description of how

age affects the strength of selection for age-specific survival and reproduction, and while he did not identify Williams' error, his derivations have allowed others to do so. While these derivations are often interpreted and developed further in terms of genetic change [7], population genetic predictions are subject to certain assumptions regarding genetic architecture. In contrast, a phenotypic selection perspective seeks to understand the relationships between fitness and phenotypes and, as such, is explicitly agnostic with respect to the genetics [13, 14, 17]. There are different modelling approaches for describing Hamilton's results using this perspective [18-20], and they all agree that selection gradients derived in this way are axiomatic. Box 1 demonstrates how Hamilton's approach proves that selection against age-specific mortality must decline with increasing adult ages.

Box 1. Why selection against age-specific mortality declines with increasing age.

Hamilton demonstrated this inevitability using implicit differentiation [11] and a definition of fitness (r) that can be applied to genes or phenotypes, where r is the **Malthusian rate of population growth** [20, 21]. An alternative is to apply conventional multivariate phenotypic selection [20, 22] approaches to individuals. This views relative fitness as a property of individuals (and only indirectly as a feature of genes or phenotypes) [13-15, 17]. Here we quantify selection acting to increase age-specific survival P_x. This can be converted to selection for age-specific mortality, μ_x, using the chain rule [23] and the definition $P_x = \exp(-\mu_x)$,

$$\frac{\mathrm{d}w}{\mathrm{d}\mu_x} = \frac{\mathrm{d}w}{\mathrm{d}P_x}\frac{\mathrm{d}P_x}{\mathrm{d}\mu_x} = -P_x\frac{\mathrm{d}w}{\mathrm{d}P_x} \qquad [1.1],$$

where w is relative fitness (defined below).

As vital rates (age-specific survival and fertility) can be correlated, selection for P_x is best quantified in a multivariate context [13], where selection is defined as a partial

covariance between relative fitness and the vital rate of interest holding all other vital rates constant. In age-structured populations with overlapping generations and stable age-distributions, the relative fitness of any individual (w_i) is the summation of its age-specific reproduction over all ages *x*, weighted by the fitness increment associated with the production of an offspring at some specified time in the future; this is the inverse of cumulative population growth $\exp(-rx)$:

$$w_i = \sum_{x=1}^{\infty} l_{xi} m_{xi} e^{-rx} \qquad [1.2],$$

where l_{xi} and m_{xi} are individual measures of cumulative survival (this is binary for individuals) and age-specific fertility. Age-specific survival is related to cumulative survival by $l_x = \prod_{z=1}^{x-1} P_z$. Because the covariance of a summation is the summation of covariances, the full covariance between relative fitness and P_x is

$$\mathrm{cov}(w, P_x) = \sum_{y=1}^{\infty} \mathrm{cov}\left(P_{xi}, l_{yi} m_{yi} e^{-ry}\right) \qquad [1.3].$$

As the partial covariance between fitness and survival at *x* holds all other vital rates constant, no covariance is generated before age $y = x + 1$. Furthermore, population means are substituted for individual measures of other vital rates: fertility values are taken from the age-specific population means, and cumulative survival at ages older than *x* are $l_{yi} = l_x P_{xi} \prod_{z=x+1}^{y-1} P_z$. Substituting into [1.3] and re-arranging, the partial covariance is

$$\mathrm{cov}(w, P_x) = \mathrm{var}_i(P_x) l_x \sum_{y=x+1}^{\infty} m_y e^{-ry} \prod_{z=x+1}^{y-1} P_z \qquad [1.4]$$

Given the relationship between cumulative and age-specific survival, it is true that $l_y / P_x = l_x \prod_{z=x+1}^{y-1} P_z$ for $y > x$. Substituting this into [1.4] and recognizing that a covariance is the product of a slope and a variance, we obtain

$$\mathrm{cov}_i(w, P_x) = \beta_{w,P_x} \mathrm{var}_i(P_x) \qquad [1.5],$$

where $\beta_{w,P_x} = \sum_{y=x+1}^{\infty} l_y m_y e^{-ry}/P_x$. From [1.1], the gradient describing selection for age-specific mortality is

$$\beta_{w,\mu_x} = -\sum_{y=x+1}^{\infty} l_y m_y e^{-ry} \quad [1.6].$$

The strength of age-specific selection is maximized and constant throughout the pre-reproductive ages but must decline over time until converging with zero at the last age of reproduction [11].

Williams' logic is partially correct. Added extrinsic mortality does reduce the fraction of the population that is exposed to selection specific to some age of interest. Furthermore, all else being equal, the strength of selection is proportional to the fraction of the population that experiences it. However, Williams' model fails to account for the fact that reductions in survival will lower population growth rates, and this enhances selection at late ages by increasing the expected fitness payoff that is realized by reaching those ages. As several theoretical studies have pointed out [5-8], the effects of decreased cumulative survival and lowered population growth rates cancel each other out exactly, and the result is that the addition of age-independent extrinsic mortality does not alter selection against age-specific mortality. While these studies use Hamilton's formal theory to comment explicitly on Williams' prediction involving selection against age-specific mortality, the same approach can be applied to reveal that added extrinsic mortality has no effect upon selection for any trait (Box 2).

Box 2. Why all phenotypic selection is insensitive to extrinsic mortality.

Phenotypic selection can be quantified as a covariance between a trait of interest, *z*, and relative fitness [24, 25]. The latter is defined for a population with age-structure and

overlapping generations in Box 1. Selection for z is therefore a summation of covariances,

$$s(z) = \sum_x \mathrm{cov}(z, l_x m_x e^{-rx}) \qquad [2.1],$$

where each covariance describes the strength of selection for trait z generated at each age x. How might that covariance in [1.3] change if the population experiences an increase in age-independent mortality $\mu_x' = \mu_x + \Delta\mu$? Assuming that this extra mortality does not affect either the trait of interest or age-specific reproduction, a change in the strength of selection must be proportional to the change in $l_x e^{-rx}$. To find this change, we first recognize that cumulative survival is a function of age-specific mortality rates, $l_x = \exp\left(-\sum_1^x \mu_y\right)$. Adding the extra source of age-independent mortality to the variable of summation and applying the product rule shows us the relationship between cumulative survival before (l_x) and after (l_x') the addition of extrinsic mortality is,

$$l_x^{'} = l_x e^{-x\Delta\mu} \qquad [2.2].$$

Second, the population growth rate r follows from age-specific rates of survival and mean reproductive rates of survivors [18, 26]. However, we are most interested in the effect of mortality upon the geometric growth rate, $\exp(r)$. Added mortality affects this rate proportional to $\exp(-\Delta\mu)$. The product yields the relationship between population growth rates before and after the added mortality. The reciprocal of its cumulative effect over x is

$$e^{-r'\mathrm{x}} = e^{-rx} e^{x\Delta\mu} \qquad [2.3].$$

Multiplying [2.2] and [2.3] shows us that the product $l_x e^{-rx}$ in the expression of phenotypic selection [2.1] is unaffected by adding age-independent mortality. **The addition of age-independent mortality can have no effect on selection for any trait.**

Models that redefine "extrinsic" to mean something else

Extrinsic mortality can be said to affect natural selection if only one changes the meaning of 'extrinsic' to mean age-dependent, but extrinsic then becomes a misnomer, because age is a property that is intrinsic to the individual. While one might question the value of retaining a term that no longer bears its original meaning, models that do this have provided valuable contributions to the evolutionary theory of aging by forcing us to consider the relationship between age and sensitivity to environmentally-derived mortality pressures. Two such investigations have been particular influential.

Density dependent population regulation

Abrams [5] considered how the ecology of mortality might make some ages more sensitive to environmental risks than others. Specifically, he asked how age-dependent density effects upon mortality might shape selection. With age-independent density effects, Abrams' models found that the addition of extrinsic mortality had no effect upon selection against mortality. In the presence of age-dependent density effects, however, causes of mortality with no direct age-specific effects reduce density pressures unequally amongst the age classes and, in this way, introduce age-specific effects on mortality indirectly. This effectively converts sources of mortality that one might consider extrinsic into age-dependent mortality. In several ecologically realistic scenarios involving added mortality, Abrams found that the strength of selection

against late-life mortality could either relax or intensify, depending upon the specific ages at which survival was most density-dependent.

There are two take-home messages from Abrams' derivations:

1. The relationship between mortality that is considered "extrinsic" in the broadest sense of the word and age-specific mortality selection can be complicated. Making even qualitative predictions regarding changes in selection requires some understanding of the specific ages at which environmental factors affect mortality and fertility and the age-specific covariances of these fitness components.
2. Density-dependent effects on survival and fertility can cause age-related changes in selection against mortality, but density-dependent population regulation cannot, by itself, cause changes in selection; some source of age-specificity is required in order for added mortality to alter selection.

The second point actually follows from the first, and it is consistent with Hamilton's notion that it is the vital rates alone that collectively define fitness [11, 19, 20]. Nevertheless, some theoreticians appear to attribute some special role of density dependent population regulation to the definition of fitness, usually by invoking Evolutionary Stable Strategy theory [27-29]. This change has been claimed to invalidate Hamilton's models in cases of density-dependent population regulation. It is not clear from these models whether they consider the definition of fitness to be changed directly by density effects or indirectly through changes in vital rates. If it is the latter, then point 2 above holds true, and Hamilton's models are generally correct. It is the former, then we need to examine whether the redefinition of fitness is justified.

210 The logic for this defense of Williams begins with the condition that density
211 regulation maintains stable population sizes with no time lag, regardless of any
212 mortality effects caused by changing density. A claim that is often made in these
213 models is that fitness itself is defined in a fundamentally different way in these stable
214 populations compared to populations that are growing or shrinking [27-29], but this is
215 neither true (at least given the individual-based phenotypic perspective considered
216 here) nor particularly relevant to the process. It is not true because fitness is defined as
217 in eq 1.2 [7, 20, 21] for all values of the population growth rate, r, even when r is zero
218 as with a stationary population. The assertion is not relevant because density
219 regulation is not limited to the case where $r = 0$; it can occur in growing or shrinking
220 populations, too. Considering its effects when $r = 0$ appears to be preferable to some,
221 presumably because it then allows us to equate relative fitness with total lifetime
222 reproduction, and this may appear to be simpler to model. Moreover, da Silva [30] has
223 argued that $r = 0$ is of special relevance in this context because populations over time
224 must have some long-term average growth rate that approximate this value. This logic
225 is problematic, because even long-term stationary populations are not invariant. They
226 are dynamically stable and must be in states of increase ($r > 0$) and decrease ($r < 0$)
227 much of the time. Fortunately, models that explicitly consider how age-independent
228 mortality affects selection in fluctuating age-structured populations with arbitrary
229 growth rates [6, 31] find no effects on selection. In summary, one should take care not
230 to conflate density dependence with the requirement that $r = 0$.

231 Continuing with the logic behind these models (and applying them to all constant
232 values of r), we imagine that mortality is added independently of age. This change
233 releases some ecological pressure that suppresses population growth, but let us
234 constrain r to be constant over time. This requirement means that some feature of the

235 population must change to compensate exactly for the growth-reducing direct effects
236 of the added mortality. One possibility considered by Williams and Day [29] is that
237 fertility is increased. Ecologically speaking, extrinsic mortality is then made to be
238 equivalent to enhanced fertility at all adult ages. Increasing adult mortality and
239 increasing fertility will shift the age structure towards younger individuals and reduce
240 selection against mortality at *all* ages, thus supporting Williams's conjecture. While
241 their model makes the further assumption that $r = 0$, this result is generally true for
242 *any* value of *r*. Williams and Day [29] suggest that "an implicit assumption in verbal
243 arguments in support of Williams' hypothesis is a notion of how density dependence
244 acts to regulate populations." That may well be a true reflection of how researchers
245 think, but this result should not be taken to mean that density dependence is sufficient
246 to support Williams' conjecture. While it does make it slightly easier to develop
247 models if one assumes that *r* is constant over time, models that permit *r* to change in
248 response to some ecological shift are not intractable (e.g., Box 3). Other than to add
249 simplicity, the only reason to hold *r* constant is to make the model yield a prediction
250 consistent with Williams. Allowing for forms of density dependence that dampen, but
251 do not eliminate, reductions in *r* associated with added mortality may not yield
252 predictions that agree with Williams.

253 Adopting again the assumption that *r* does not change after the addition of extrinsic
254 mortality, we may ask if increased fertility is the only way that density dependence
255 can achieve this condition. Here we are confronted with the conceptual issue of what
256 exactly defines extrinsic mortality. A theoretician may define the extrinsic mortality
257 to be an effect, in the sense that something has changed in the population that has
258 resulted in an age-independent increase in mortality. However, an experimenter might
259 view it as a treatment; for example, an experiment might randomly destroy some

fraction of individuals within a population. If survival at different ages responds differently to the relaxed density effects triggered by an application of imposed age-independent mortality, then the two definitions can diverge. Depending upon the ecology of density dependence specific to some population, it could be that an extrinsic mortality experiment with density dependence achieves stable r values by indirectly imposing a net survival advantage either for younger or for older individuals. Following the findings of Abrams (1993), the former will yield predictions consistent with Williams, and the latter will predict the opposite.

Condition-dependent mortality

Williams and Day [29] asked what might happen if some ages were less able to successfully cope with environmental change than other ages. These more sensitive ages are considered to have a poorer "condition", and by this definition, the mortality interaction between age and environment is termed **condition-dependent mortality**. The scenario in which condition declines with increased age is of interest, because this fits well with what we know about the relative frailty of older individuals, and it leads to the same prediction as Williams' verbal model. However, the very young can also be relatively frail, and when the most sensitive individuals are the youngest, this model predicts the opposite of Williams' model.

While Abrams's models are ecologically motivated by hypothetical effects of density, and Williams and Day's models add realism to the physiological costs of age to environmental challenges, the fundamental relationship between changes in age-specific mortality and changes in selection against age-specific mortality are unchanged and adequately predicted by Hamilton's equations. To illustrate this, the model in Box 3 asks the relevant question in its most fundamental form possible: if we increase mortality by some specific amount at age x, what will happen to the

strength of selection against mortality at age *y*? This model is agnostic both to the cause of this added mortality and to the nature of the genetic architecture underlying age-specific mortality. It recapitulates predictions from Abrams' and Williams and Day's models; namely, that added mortality that is focused upon early ages increases selection at late age, and added mortality focused upon older ages decreases selection in late-life. While the latter observation may appear superficially to be identical to Williams's prediction, it is not: increased adult mortality rates are not a sufficient condition for relaxed selection against adult mortality. It is a requirement that juvenile mortality is affected *less*. We note that similar results to these have recently been derived using a population projection matrix approach [31].

Box 3. Why added age-specific mortality can both increase and decrease selection against late-life mortality.

Here it is convenient to change notation from the discrete to the continuous case. Selection for mortality at age *x* is

$$\beta_{w\mu_x} = -\int_x^\infty l_y m_y e^{-ry} dy \qquad [3.1].$$

The change in selection following increased mortality follows the differential taken with respect to age-specific mortality. Following the chain rule,

$$\frac{\mathrm{d}\beta_{w\mu_x}}{\mathrm{d}\mu_{x'}} = -\int_x^\infty l_y m_y \frac{\mathrm{d}e^{-ry}}{\mathrm{d}\mu_{x'}} dy - \int_x^\infty m_y e^{-ry} \frac{\mathrm{d}l_y}{\mathrm{d}\mu_{x'}} dy \qquad [3.2].$$

This change has two causes. First, added mortality reduces the rate of population growth. The differential in the first integral can be expressed using the first derivative of growth rate taken with respect to the added mortality, $\mathrm{d}\exp(-ry)/\mathrm{d}\mu_{x'} = -y\exp(-ry)\,\mathrm{d}r/\mathrm{d}\mu_{x'}$. This new differential is Hamilton's indicator of selection (see [1.5]). Substituting these into the first term on the right-hand side of [3.2],

$$-\int_x^\infty l_y m_y \frac{\mathrm{d}e^{-ry}}{\mathrm{d}\mu_{x'}} dy = -\frac{\int_{x'}^\infty l_y m_y e^{-ry} dy}{T} \int_x^\infty y l_y m_y e^{-ry} dy \quad [3.3],$$

where $T = \int_0^\infty y l_y m_y e^{-ry} dy$ is both the mean age of new parents (assumed for simplicity to be hermaphrodite) and one measure of generation time [7]. Equation [3.3] is negative, and its effect will always be to intensify selection at all ages. The second effect comes from a reduction in cumulative survival after age x'. At these older ages, the change in cumulative survival is the product of the initial cumulative survival and the added risk of death, $\mathrm{d}l_x/\mathrm{d}\mu_{x'} = -l_x \exp(-\mu_{x'})$. As the differential assumes an infinitesimal change, this can be approximated as $\mathrm{d}l_x/\mathrm{d}\mu_{x'} \approx -l_x$. It follows that

$$-\int_x^\infty m_y e^{-ry} \frac{dl_y}{d\mu_{x'}} dy = \begin{cases} 0, & x < x' \\ \int_x^\infty l_y m_y e^{-ry} dy, & x \geq x' \end{cases} \quad [3.4].$$

This contribution acts to weaken selection by adding a positive to a negative, and the complete change [3.2] for older individuals is the sum of [3.3] and [3.4].

When constrained to be positive, this sum reveals the conditions under which the strength of selection against age-specific mortality must weaken with added mortality. With some re-arrangement,

$$\frac{\int_x^\infty l_y m_y e^{-ry} dy}{\int_{x'}^\infty l_y m_y e^{-ry} dy} > \frac{\int_x^\infty y l_y m_y e^{-ry} dy}{\int_0^\infty y l_y m_y e^{-ry} dy} \quad [3.5].$$

The left-hand side of [3.5] converges on 1 as $x' \to x$, and the inequality at this limit becomes,

$$\int_0^\infty y l_y m_y e^{-ry} dy > \int_x^\infty y l_y m_y e^{-ry} dy \quad [3.6].$$

This condition is always met provided that *x* is an age greater than the first age of reproduction. **Selection against late-life mortality weakens when new mortality is added at slightly younger ages.**

Selection against age-specific mortality intensifies when the sum of [3.3] and [3.4] is negative. Let us assume that mortality is added to some pre-reproductive age x'. Reversing the inequality in [3.5] and noting that $\int_{x'}^{\infty} l_y m_y e^{-ry} dy = 1$, stronger selection is shown to follow at all later ages that satisfy,

$$T < \frac{\int_x^{\infty} y l_y m_y e^{-ry} dy}{\int_x^{\infty} l_y m_y e^{-ry} dy} \qquad [3.7].$$

Recall that *T* is the average age of new parents in the entire population. Because, the right-hand side of [3.7] is the average age of new parents *older* than *x*, [3.7] is satisfied for all ages beyond the onset of reproduction. **Adding mortality only to juveniles increases selection against adult mortality.**

Comparative studies of the relationship between extrinsic mortality and senescence

For centuries [32] [33], attempts to understand aging have used a comparative approach. Comparative studies of senescence typically test for the negative correlations expected from antagonistic pleiotropy [34-36], or compare measures of aging (typically, maximum observed lifespan) with behavioral, life history or ecological traits [37-40]. They commonly conclude that Williams [4] was right: rates of aging are positively correlated with 'fast' life histories and high extrinsic mortality (Table 1). Since Williams' model is flawed (see above), at best one can conclude that Williams was right for the wrong reasons. The challenge is to determine the true cause of this apparent support for Williams.

We suggest four factors that complicate comparative efforts to relate extrinsic mortality and aging, and for studies that offer putative support for Williams' conjecture, we provide plausible alternative interpretations (see Table 1). First, putative sources of "extrinsic mortality" are actually age-dependent in ways that favor the evolution of senescence patterns following Hamilton's fundamental model (i.e., Box 3). Consider long-lived marine bivalves [41] such the ocean quahog *Arctica islandica*, which can live for more than 500 years [42, 43]. Their hard shells and fossorial habit might seem consistent with low extrinsic mortality. However, while adult mortality is as low as 2%, recruitment failure is common [44]. Theory predicts that this should select strongly for low senescence throughout adult life (Box 3).

Second, while life tables that quantify age-specific mortality exist for many species, it is not clear how to accurately measure extrinsic mortality. Parametric models such as the Gompertz [34] or Weibull [45] have been used to estimate minimum mortality, but one must use caution in equating parametric estimates of minimum mortality with extrinsic mortality. Some have argued that captive populations can be used to measure **actuarial senescence** in the absence of extrinsic mortality. However, these populations may experience unnatural sources of mortality, such as inadequate micronutrients, novel pathogens, lack of commensal heterospecifics, space constraints. Even if we could putatively measure extrinsic and intrinsic mortality in the wild [46], the two are not separable if internal condition interacts with the effects of extrinsic mortality [29].

Third, comparative studies typically assume that short lifespan means high aging and long lifespan means low aging, but one can have a very short lifespan with no aging [47], or the reverse. Mean and maximum lifespan (MLS) are not measures of aging, nor is either a good proxy for aging [48-50]. In fact, if the only force of mortality

acting on a population were age-independent extrinsic mortality ($\Delta\mu$), then we could calculate mean lifespan $e_o = 1/(1-\exp(-\Delta\mu))$. In this case, we would expect lifespan and extrinsic mortality to be negatively associated by definition. Following from this relationship, and a definition of short lifespan as equivalent to high aging, then even in the complete absence of senescence, we would observe apparent support for Williams [4].

Finally, although there are many examples of a negative correlation between lifespan and the apparent extrinsic risk of death faced by an organism, this risk is more often inferred than measured (Table 1). For example, Keller and Genoud [38] showed that eusocial queen ants are extraordinarily long lived compared to their non-eusocial relatives. They argue that this finding is consistent with Williams [4], because (they assume) eusocial species have lower extrinsic mortality than non-eusocial species. But without rigorous tests, this assumption is not necessarily true [51]. In the case of the eusocial naked mole rats (*Heterocephalus glaber*) [52], Williams and Shattuck [53] note that the association between eusociality and lifespan might be due to the effect of eusociality itself, rather than fossoriality, a suggestion supported by the data [52].

Concluding remarks and looking forward

We have shown how added age-dependent mortality can alter age-specific selection and how that mortality can, in turn, affect the evolution of aging (Box 3). Three specific challenges need to be addressed in evolutionary comparative studies of aging.

First, to explain why organismal fitness components decline with age, we need to study the actual phenomenon of aging, not its proxies, such as mean and maximum lifespan. We should measure age-related rates of decline in fitness components

399 (survival and reproduction), or in traits associated with fitness, such as behavior,
400 physiological performance, or disease risk. We then need to standardize these
401 measures to accommodate the vastly different life-histories seen across taxa. Among
402 several possible scaling factors [48], for evolutionary applications, we prefer mean
403 generation time (defined in Box 3), because it best encapsulates the time scales of
404 evolutionary change. It is the time interval that separates parents and offspring, whose
405 phenotypic resemblance provides the most sensible expression of inheritance, and
406 among the various proposed scaling factors, mean generation time is the one found in
407 Hamilton's descriptions of selection [11].

408 Among studies that do measure rates of change in mortality, we still face the
409 challenge of how to parameterize these measures. Early on, Promislow [34] argued
410 for the slope of the Gompertz curve as a measure of demographic aging. We see this
411 mortality pattern among animal species representing almost a billion years of
412 evolutionary divergence, in both lab and natural settings, and Gompertz-type aging in
413 adults is predicted from population genetic theory [54]. However, Baudisch [55] has
414 argued that these predictions are based upon arbitrary assumptions regarding the scale
415 at which new mutations act upon mortality, and that other shapes of aging might be
416 expected to evolve under other genetic assumptions. In addition, Ricklefs [45]
417 combined two parameters from the Weibull model to introduce a widely-cited
418 alternative measure of aging. More theory and careful genetic measurements in
419 diverse environments are needed to identify the best metric for demographic aging.

420 Second, as we have argued, the 'right' question is not whether aging is correlated with
421 extrinsic mortality. Rather, we need to investigate whether age-related changes in
422 selection intensity adequately predict patterns in nature across species, ecological
423 settings and within species. Whether (and how) other factors such as arboreality,

toxicity, or sociality feed into vital rates and thereby shape selection intensities is an open and interesting question for future study.

Finally, we encourage researchers to be more circumspect in their interpretation of empirical comparative patterns. We are excited by the findings that mean lifespan appears to be greater in flying and arboreal than in terrestrial mammals [39, 56], in toxic than in non-toxic amphibia [37], and in eusocial than in non-eusocial species [38, 52, 53] (Table 1). But these findings should mark the beginning of our exploration of the forces that shape lifespan, and they should prompt us to ask if these patterns are also associated with aging, without assuming that they are.

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Glossary

Actuarial senescence An age-related increase in mortality risk.

Antagonistic pleiotropy A property of mutations that have beneficial effects in early life and deleterious effects later in life.

Condition-dependent mortality A correlation between the mortality rate and a biological state, such as size, sex or nutritional status.

Evolutionary Theory of Senescence The theory, originally due to PB Medawar and later formalized by WD Hamilton, that **senescence** is the result of a decrease in the force of natural selection with age (See Box 1).

Malthusian rate of population growth A key parameter r in a model of population growth described by the form $N(t) = N(0)e^{rt}$.

Senescence A degradation of biological function in older individuals most conspicuously manifested as increased risk of mortality or decreased fertility.

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Table 1. Reinterpretation of studies of aging that claim to support (or fail to support) the extrinsic mortality (EM) hypothesis using Hamilton's perspective. The allometric effect of body size on lifespan is usually controlled for and is not listed as an independent variable here.

Organism	Reference	Type of study: Experimental/ Comparative/ Observational	Independent variable(s)	Source of EM	Main reported effects of EM on life history	Reinterpretation
Arthropoda: *Daphnia*	[57], [58]	Observational	Temporary ponds *vs.* permanent lakes	Habitat deterioration	Shorter life and reproductive lifespan in temporary habitats	Habitat deterioration occurs at the end of the season and is therefore likely to affect late life stages more than early ones. This would

						select for the observed pattern
Arthropoda: *Daphnia ambigua*	[59]	Observational	Predation pressure varied among lakes, depending on presence of predatory fish	Severity and duration of fish predation	No difference in lifespan among populations from lakes with different mortality risks	In this system, fish predation does not alter the distribution of the mortality risk with age of prey
Arthropoda: *Drosophila*	[60]	Experimental evolution	High *vs.* low mortality treatments at constant	Experimental culling treatment	A 7% difference in lifespan evolved after 50 generations of experimental selection	Selection was on adult flies, not larvae, so the applied mortality treatment was not independent of age and the result, though modest, is

			population density			consistent with Hamilton's theory.
Arthropoda: Hymenoptera	[38]	Comparative	Eusociality	Predation (presumed)	Reproductive castes of eusocial insects have lifespans 100-fold greater than other castes from the same species.	Predicted if eusociality increases the survival of reproductive adults more than larvae or delays the production of fertile offspring. Also predicted if eusociality increases the survival rate of older queens vs. younger queens.

Birds	[61]	Comparative	Diet, insular breeding habitat & sociality	Predation (presumed)	Maximum longevity in the wild greater in herbivores than carnivores, in birds that breed on islands & those living socially	Predicted if diet, insular breeding & sociality increases the survival of adults more than juveniles
Birds	[62]	Comparative	Species richness of predatory birds	Predation by birds (presumed)	Lifespan is longer in regions with lower species richness of predatory birds	Lifespan follows proximately from mortality risk. There is no need to invoke evolution.

Fish: *Nothobranchius furzeri*	[63]	Observational	Temporary pool habitats varied in how long they persisted	Habitat deterioration	Shorter lifespan and faster physiological aging in pools of shorter duration	Habitat deterioration affects mortality of adults, but not juveniles because the latter survive in a dormant resting stage [64]. This would select for the observed pattern.
Herps & fishes	[37]	Comparative	Poisonous *vs.* non-poisonous species	Predation in the wild (presumed)	Adjusted for body size, poisonous species live longer in captivity than non-poisonous in the same taxon	Predicted if poisonousness increases the survival of adults more than juveniles

Herptiles	[65]	Comparative	Poisonous *vs.* non-poisonous species	Predation (presumed)	Chemically protected amphibians live longer than unprotected species but venomous snakes do not live longer than non-venomous ones	The observed pattern in amphibians is predicted if chemical protection increases the survival of adults more than juveniles.
Mammal: American opossum	[66]	Observational	Presence on mainland/ absence on an island (presumed)	Predation	Earlier maturation and shorter life	Predicted if predation differentially affects older animals, but this cannot be determined just from the

						presence or absence of predators.
Mammals	[39]	Comparative	Arboreal *vs.* terrestrial species	Predation (presumed)	Arboreal mammals live longer than terrestrial ones	Predicted if arboreality decreases adult mortality greater than juvenile mortality.
Terrestrial vertebrates	[67]	Comparative	EM variation analyzed at family level across mammals, birds and herptiles.	Unknown. EM was taken to be the mortality rate experienced by young adults that were presumed to be non-senescent	EM accounted for 22% of the variance in actuarial senescence	Since EM was a mortality rate measured in adults, this result is consistent with Hamilton's theory

Terrestrial vertebrates	[68]	Comparative	Flight, arboreality, fossoriality	Predation (presumed)	Flying, arboreal & fossorial living are each associated with longer lifespan	Predicted if flight, arboreal and fossorial living increase the survival of adults more than juveniles

Highlight & Outstanding Questions entered here for mark-up purposes.

Highlights

- The evolutionary theory of senescence underpins research in life history evolution and the biology of aging.
- G.C. Williams predicted that higher death rates select for earlier senescence and shorter length of life. A corollary is that senescence should be correlated with age-independent, or 'extrinsic' mortality.
- We review the formal, mathematical theory that shows that Williams' verbal model is wrong.
- Williams' idea has nonetheless prospered because it offers an intuitively appealing explanation for patterns that are widely observed in nature.
- We offer alternative explanations for the comparative patterns that are consistent with W.D. Hamilton's formulation of the evolutionary theory of senescence.
- A wider appreciation of how empirical patterns can be explained by the formal evolutionary theory of senescence should stimulate new research.

Outstanding Questions

1. The goal of all evolutionary theories of aging is to explain why organismal fitness components decline with age. We need to study the actual phenomenon of aging, not its proxies, but we do not yet have cogent arguments for what the appropriate metric of aging is. More theory and careful genetic measurements taken in many species under many different environments are likely required to identify what the appropriate metric for demographic aging should be.

2. The 'right' question is not whether aging is correlated with extrinsic mortality, but rather: Does Hamilton's model for age-related changes in selection intensity adequately predicts patterns in nature? This requires that one actually measure selection intensity at different ages and in multiple species or in different populations

of the same species found in different ecological settings. Whether (and how) other factors such as arboreality, toxicity, or sociality shape selection intensities is an open and interesting question for future study.

3. We encourage researchers to be more circumspect in their interpretation of empirical comparative patterns. We are excited by the findings that mean lifespan appears to be greater in flying and arboreal than in terrestrial mammals, in toxic than in non-toxic amphibia and in eusocial than in non-eusocial species (Table 1). But we need to ask whether these patterns are also associated with aging, without assuming that they are.